DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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Silver Spring, MD 20993-0002

SEEGENE
C/O FRAN WHITE, REGULATORY CONSULTANT
MDC ASSOCIATES, LLC
180 CABOT STREET
BEVERLY MA 01915

August 17, 2015

Re: K142156
Trade/Device Name: Anyplex™ II HSV-1/2 Assay
Regulation Number: 21 CFR 866.3305
Regulation Name: Herpes Simplex Virus Nucleic Acid Amplification Assay
Regulatory Class: II
Product Code: OQO
Dated: February 10, 2015
Received: February 11, 2015

Dear Dr. White:

This letter corrects our substantially equivalent letter of February 13, 2015.

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of

medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Stephen J. Lovell -S for

Uwe Scherf, M. Sc., Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics
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Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K142156

Device Name
AnyplexTM II HSV-1/2 Assay

Indications for Use *(Describe)*
The AnyplexTM II HSV-1/2 Assay is a real-time polymerase chain reaction (PCR)-based in vitro diagnostic test intended for the qualitative detection and differentiation of Herpes Simplex Virus Type-1 (HSV-1) and Herpes Simplex Virus Type-2 (HSV-2) DNA from female skin lesions from anogenital sites. The test is intended for use as an aid in the diagnosis of anogenital HSV infection in symptomatic patients.

WARNING: The AnyplexTM II HSV-1/2 Assay is not indicated for use with cerebrospinal fluid (CSF). The assay is not intended to be used for prenatal screening.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

Date of Summary: February 9, 2015

Product Name Anyplex™ II HSV-1/2 Assay

Sponsor
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Correspondent
MDC Associates, LLC
Fran White, Regulatory Consultant
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Device Identification

Trade or Proprietary Name: Anyplex™ II HSV-1/2 Assay

Common or Usual Name: HSV-1/2 Assay

Product Code: OQO

Regulation Section: 21 CFR 866.3305

Product Classification: Class II

Intended Use

The Anyplex™ II HSV-1/2 Assay is a real-time polymerase chain reaction (PCR)-based *in vitro* diagnostic test intended for the qualitative detection and differentiation of Herpes Simplex Virus Type-1 (HSV-1) and Herpes Simplex Virus Type-2 (HSV-2) DNA from female skin lesions from anogenital sites. The test is intended for use as an aid in the diagnosis of anogenital HSV infection in symptomatic patients.

WARNING: The Anyplex™ II HSV-1/2 Assay is not indicated for use with cerebrospinal fluid (CSF). The assay is not intended to be used for prenatal screening.

Device Description

The Anyplex™ II HSV-1/2 Assay uses PCR to generate amplified product from HSV-1 and HSV-2 present in clinical specimens. The presence of HSV-1 and/or HSV-2 target DNA is indicated by the fluorescent signal generated through the use of fluorescently-labeled oligonucleotide probes (duplex Catcher) on the Cepheid SmartCycler® II Dx instrument. The

probes do not generate a signal unless they are specifically bound to the amplified product. A preparation of HSV-1 and HSV-2 plasmids is included as the positive control in the Anyplex™ II HSV-1/2 Assay. Run as a separate control, the positive control serves to demonstrate that the HSV-1/2 PCR reagents are functional, and discriminate the validity of the run. In addition, the positive control functions as a process control, demonstrating that sample preparation has proceeded correctly during the run. An internal control (IC) is also included in the assay kit. The IC is added to each sample specimen during sample preparation, and is also used to create a Blank Negative Control by adding a set amount to viral transport media to serve as an extraction control. In addition, the RNase-free water is used to create the Negative Control by adding a set volume to the prepared master mix. Users are instructed to include all three controls, Positive, Negative, and Blank Negative Control with each test run.

Substantial Equivalency

The Anyplex™ II HSV-1/2 Assay is substantially equivalent to the IMDx HSV-1/2 for Abbott *m*2000 assay. Table 1 compares the characteristics of the Anyplex™ II HSV-1/2 Assay (New Device) and the IMDx HSV-1/2 for Abbott *m*2000 assay (Predicate Device).

Table 1: Substantial Equivalence

Similarities		
Characteristic	**IMDx HSV-1/2 for Abbott *m*2000 Assay (Predicate Device)**	**Anyplex™ II HSV-1/2 Assay (New Device)**
510(k)	K140198	K142156
Regulation	21 CFR 866.3305	21 CFR 866.3305
Product Code	OQO	OQO
Device Class	Class II	Class II
Intended use	The IMDx HSV-1/2 for Abbott *m*2000 assay is an *in vitro* diagnostic test for the direct, qualitative detection and differentiation of herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2) DNA from male and female skin lesions from anogenital or oral sites. The test is intended for use as an aid in the diagnosis of HSV infection in symptomatic patients. The assay is intended to be run on the Abbott *m*2000 instrument system. ***Warning:*** The IMDx HSV-1/2 for Abbott *m*2000 assay is not FDA cleared for use with cerebral spinal	The Anyplex™ II HSV-1/2 Assay is a real-time polymerase chain reaction (PCR)-based *in vitro* diagnostic test intended for the qualitative detection and differentiation of Herpes Simplex Virus Type-1 (HSV1) and Herpes Simplex Virus Type-2 (HSV2) DNA from female skin lesions from anogenital sites. The test is intended for use as an aid in the diagnosis of anogenital HSV infection in symptomatic patients. **WARNING: The Anyplex™ II HSV-1/2 Assay is not indicated for use with cerebrospinal fluid (CSF). The**

Similarities		
Characteristic	**IMDx HSV-1/2 for Abbott *m*2000 Assay (Predicate Device)**	**Anyplex™ II HSV-1/2 Assay (New Device)**
	fluid (CSF) or for pre-natal screening.	**assay is not intended to be used for prenatal screening.**
Test Principle	Real-time PCR DNA amplification	Real-time PCR DNA amplification
Assay Results	Qualitative detection and differentiation of HSV-1 and HSV-2	Qualitative detection and differentiation of HSV-1 and HSV-2
Differences		
Characteristic	**IMDx HSV-1/2 for Abbott *m*2000 Assay (Predicate Device)**	**Anyplex™ II HSV-1/2 Assay (New Device)**
Instrumentation	Sample extraction and real-time PCR amplification/detection using the Abbott *m*2000 system.	Real-time PCR amplification/detection using the Cepheid SmartCycler II DX system.
Extraction Method	Automated on Abbott *m*2000 system	Manual extraction using the QIAGEN QIAamp® DNA Mini Kit
Detection Method	Double-labeled (fluorophore and quencher) hydrolysis probes. Measures increase in assay fluorescence with each PCR cycle.	Double-labeled (fluorophore and quencher) duplex Catcher. Measures increase in assay fluorescence with each PCR cycle.
Sample type	Male and female skin lesions from anogenital or oral sites	Female skin lesions from anogenital sites only

Performance Characteristics

Analytical Performance

Precision/Repeatability:

A precision study was conducted in-house by testing 5 different panels consisting of HSV-1/2 Negative, HSV-1 Low Positive (1X LoD), HSV-1 High Positive (10X LoD), HSV-2 Low Positive (1X LoD) and HSV-2 High Positive (10X LoD). All panels were tested twice per day for twenty days by one operator. Samples were tested in triplicates for each run (for a total of 600 data points for the 40 runs).

Table 2: Precision Study Average Ct Values

Panel Member	Level	Agreement with expected results	95% Confidence Interval	Avg. Ct	SD Ct	%CV Ct
HSV-1 Low Positive	1X LoD	100.00% (120/120)	96.90% - 100.00%	42.93	0.75	1.74%
HSV-1 High Positive	10X LoD	100.00% (120/120)	96.90% - 100.00%	40.32	0.71	1.76%
HSV-2 Low Positive	1X LoD	100.00% (120/120)	96.90% - 100.00%	41.31	1.06	2.56%
HSV-2 High Positive	10X LoD	100.00% (120/120)	96.90% - 100.00%	38.19	0.51	1.34%
Negative	N/A	100.00% (120/120)	96.90% - 100.00%	N/A	N/A	N/A

* Mean: Average Ct of positive results only.

Precision/Reproducibility Results

Reproducibility studies were performed at three sites (one internal and two external clinical sites) using 3 lots of the reagent kits. Each test site tested one lot of the reagent kit. The test panel of seven members was prepared blinded and randomized and tested for five (5) days non-consecutive days by two operators with each operator running the panel, in triplicate, once a day. Variables in the reproducibility study included between run-to-run, operator-to-operator, site-to-site and lot-to-lot.

Table 3 below shows the Percent (%) Agreement and Average of Ct for each site as well as the Total (%) agreement and Average of Ct for all 3 sites combined.

Table 3: Reproducibility Study Summary

		Site 1		Site 2		Site 3		All 3 sites Combined	
Panel Member	**Concentration**	**% Agreement** *Agreement with expected result*	**Avg. Ct (%CV)**	**% Agreement** *Agreement with expected result*	**Avg. Ct (%CV)**	**% Agreement** *Agreement with expected result*	**Avg. Ct (%CV)**	**% Agreement** *Agreement with expected result*	**Avg. Ct (%CV)**
HSV-1 High-Positive*	3X LoD	100.0% 30/30	36.4 (2.0%)	100.0% 30/30	35.9 (2.6%)	100.0% 30/30	36.1 (2.9%)	100.0% 90/90	36.1 (2.6%)
HSV-1 Low-Positive*	1X LoD	100.0% 30/30	39.9 (2.2%)	90.0% 27/30	39.8 (3.3%)	100.0% 30/30	39.2 (1.7%)	96.67% 87/90	39.6 (2.6%)
HSV-1 High-Negative**	<1X LoD	6.67% 2/30	42.9 (3.2%)	43.33% 13/30	42.6 (3.9%)	3.33% 1/30	42.4 (2.4%)	17.78% 16/90	42.6 (3.1%)
HSV-2 High-Positive*	3X LoD	100.0% 30/30	36.5 (1.6%)	100.0% 30/30	35.7 (2.2%)	100.0% 30/30	36.4 (1.7%)	100.0% 90/90	36.2 (2.0%)
HSV-2 Low-Positive*	1X LoD	100.0% 30/30	39.8 (2.3%)	93.3% 28/30	39.6 (2.4%)	100.0 30/30	39.9 (2.4%)	97.8% 88/90	39.8 (2.3%)
HSV-2 High-Negative**	<1X LoD	30.0% 9/30	42.3 (2.8%)	46.67% 14/30	42.1 (4.0%)	16.67% 5/30	42.2 (2.5%)	31.1% 28/90	42.2 (3.0%)
HSV Negative**	N/A	100.0% 60/60	0.0	98.33% 59/60	42.7	100.0% 60/60	0.0	99.4% 179/180	42.7

*Expected result is positive. %CV calculated from results with non-zero Ct values.

** Expected result is negative. %CV calculated from results with non-zero Ct values.

Analytical Sensitivity (Limit of Detection)

The LoD is determined as the HSV-1/2 titer ($TCID_{50}$/mL) detected with a positivity rate of 95% or greater. The LoD of the Anyplex™ II HSV-1/2 Assay was determined for two strains of HSV-1 and two strains of HSV-2. The results, representative of the analytical sensitivity of the Anyplex™ II HSV-1/2 Assay, are summarized in Table 4.

Table 4: Limit of Detection

Strain	Limit of Detection (95% CI)
HSV-1 MacIntyre	$3.75X10^2$
HSV-1 HF	$1.88X10^2$
HSV-2 MS	$3.75x10^1$
HSV-2 G	$3.75x10^1$

Cross-Reactivity and Microbial Interference

A panel of 50 organisms was tested for cross-reactivity and interference with the Anyplex™ II HSV-1/2 Assay. Intermediate stocks of bacteria, yeast, viruses, and organism genomic DNA were prepared from quantitated stocks and then diluted to their final test concentration. All samples were prepared by diluting organisms or DNA into M4 viral transport medium. No strains tested were positive for HSV-1 or HSV-2 using the Anyplex™ II HSV-1/2 Assay.

Table 5: Cross-Reactivity and Microbial Interference Panel

Organism	Organism
Atopobium vaginae	*Gardnerella vaginalis*
Bacteroides fragilis	Human Herpes 6B virus (Z29 strain)
Candida albicans	Human Herpes 7 virus (SB strain)
Candida glabrata Z007	Human Papilloma virus-16 (Caski)
Candida guilliemondii Z008	Human Papilloma virus-18 (Hela)
Candida krusei Z009	*Klebsiella pneumoniae* Z026
Candida lusitaniae Z010	*Lactobacillus acidophlus*
Candida parapsilosis Z011	*Lactobacillus crispatus*
Candida tropicalis Z012	*Lactobacillus gasseri*
Chlamydia trachomatis (D-UW3)	*Lactobacillus jensenii*
Chlamydia trachomatis (serotype E)	*Moraxella catarrhalis* Ne 11
Chlamydia trachomatis (serotype F)	*Mycoplasma hominis*
Chlamydia trachomatis (serotype G)	*Neisseria gonorrhoeae*
Chlamydia trachomatis (serotype H)	Rubella virus
Chlamydia trachomatis (serotype I)	*Serratia marcescens*
Chlamydia trachomatis (serotype J)	*Staphylococcus saprophyticus*
Chlamydia trachomatis (serotype K)	*Streptococcus mitis*
Cytomegalovirus (AD169)	*Streptococcus mutans* Z072

Organism	Organism
Enterococcus casseliflavus	*Streptococcus oralis*
Enterococcus faecalis	*Streptococcus pneumoniae* 19F
Enterococcus faecium	*Streptococcus pyogenes* Rosenbach
Enterococcus gallinarum	*Toxoplasma gondii*
Enterovirus (Type 71)	*Trichomonas vaginalis*
Epstein-Barr virus (B95-8 strain)	*Ureaplasma urealyticum*
Escherichia coli	Varicella Zoster virus

Interfering Substances

The interference study was conducted with the Anyplex™ II HSV-1/2 assay using a panel of twenty two (22) interfering substances that could be present in the female anogenital swab lesion specimens and interfere with the performance of the Anyplex™ II HSV-1/2 assay.

The interfering substances were tested at concentrations at or above physiological levels or typical usage levels with HSV strains (HSV-1 MacIntyre and HSV-2 MS) at 3X LoD. None of the 22 substances showed detectable effect of interference, resulting in all samples being positive for HSV1 or HSV2.

Clinical Performance Characteristics

The performance of the Anyplex™ II HSV-1/2 Assay was evaluated at three geographically-diverse locations within the United States from 2013-2014. A total of 656 valid specimens was included in the final data set and analyzed for product performance as compared to results obtained from the ELVIS® (Enzyme Linked Virus Inducible System) HSV ID and D^3 Typing Test System (Diagnostic Hybrids, Athens, OH). The reference ELVIS viral culture method used in this study is unable to detect co-infected specimens and cannot identify HSV-1 if HSV-2 is identified first. Consequently, if a specimen was positive for HSV-2, it was removed from the calculation of the HSV-1 clinical performance.

Assay performance for anogenital specimens is shown below for the 656 prospective specimens included in the study.

Table 6: HSV-1 Anogenital Results

HSV-1 Performance		Reference Method		
		POS	NEG	Total
Anyplex™ II HSV-1/2 Assay	POS	91	29[a]	120
	NEG	1[b]	429	430
	Total	92	458	550
Sensitivity; 95% CI		98.9% (91/92); 95% CI [94.1%-99.8%]		
Specificity; 95% CI		93.7% (429/458); 95% CI [91.0%-95.6%]		

[a] Discordant analysis (bidirectional sequencing) was performed on all 29 samples identified as HSV-1 positive by the Anyplex™ II HSV-1/2 Assay. HSV-1 was detected in 18 of the 29 samples. The remaining 11 specimens remained discordant (HSV-1 was not detected).
[b] Discordant analysis (bidirectional sequencing) was performed on the one sample identified as negative by the Anyplex™ II HSV-1/2 Assay. HSV-1 was detected in this sample.

Table 7: HSV-2 Anogenital Results

HSV-2 Performance		Reference Method		
		POS	NEG	Total
Anyplex™ II HSV-1/2 Assay	POS	103	35[c]	138
	NEG	3[d]	515	518
	Total	106	550	656
Sensitivity; 95% CI		97.2% (103/106); 95% CI [92.0%-99.0%]		
Specificity; 95% CI		93.6% (515/550); 95% CI [91.3%-95.4%]		

[c] Discordant analysis (bidirectional sequencing) was performed on all 35 discordant specimens identified as HSV-2 positive by the Anyplex™ II HSV-1/2 Assay. HSV-2 was detected in 21 of the 35 specimens. The remaining 14 remained discordant (HSV-2 was not detected).
[d] Discordant analysis (bidirectional sequencing) was conducted for the three specimens identified as HSV-2 negative by the Anyplex™ II HSV-1/2 Assay. HSV-2 was not detected in any specimen.

Conclusions

The submitted information in this premarket notification is complete and supports a substantial equvalence decision.